

## REMARKS

This Amendment is submitted in response to the final Office Action dated January 13, 2004. Claims 1, 4, 5, 12, 15 and 16 are pending in the application. Claims 1, 4, 5, 12, 15 and 16 are rejected. A Petition for a Two-Month Extension of Time to Respond to the Office Action and a check in the amount of \$210 to cover the fees of the two-month extension are also submitted herewith. Please charge Deposit Account No. 02-1818 for any insufficiency or credit for any overpayment.

Claims 1 and 12 have been amended to further define the claimed invention, and it is respectfully submitted that the amendments add no new subject matter.

Support for the amendment requiring a culture of neural precursor cells in serum free medium "including a first mitogen" can be found in the Specification at, for example, the last paragraph of page 12 which carries over onto page 13 of the Specification.

Support for the amendment requiring introducing a *c-myc* construct and a selectable marker into "a cell of the adhesion culture in serum free medium including a first mitogen" can be found in the Specification at, for example, the last paragraph of page 12 which carries over onto page 13 and at the last sentence in the second paragraph on page 10 of the Specification.

Support for the amendment requiring culturing the cells "including the *c-myc* construct" in a medium including the first mitogen and a second mitogen can be found in the Specification at, for example, the first full paragraph on page 13 of the Specification.

Claims 1, 4, 5, 12, 15 and 16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Nakafuku et al. ("*Nakafuku*") in view of U.S. Patent No. 5,851,832 to Weiss et al. ("*Weiss*"). Applicants respectfully submit that the cited references fail to teach or disclose each element of the claimed invention either alone or in combination. Moreover, Applicants respectfully submit the combination of *Weiss* with *Nakafuku* is improper.

As amended, independent claims 1 and 12 are directed to a method for producing stable cell lines of mammalian neural precursor cells *in vitro*. The method requires, among other steps, preparing an adhesion culture of neural precursor cells in a serum-free medium including a first mitogen and introducing a *c-myc* construct into a cell in that adhesion culture. The method also requires culturing the cells including the *c-myc* construct in a medium containing the first mitogen and a second mitogen that is "other than the first mitogen." That medium also contains

a *c-myc* activating chemical such as  $\beta$ -estradiol, RU38486, dexamethasone, thyroid hormones, retinoids, and ecdysone.

*Nakafuku* fails to disclose preparing an adhesion culture of neural precursor cells in a serum-free medium including a first mitogen as required by claims 1 and 12 of the claimed invention. In *Nakafuku*, at least prior to and during the introduction of the myc-derived gene to precursor cells, the cells are cultured in a medium containing serum and without added mitogen. Furthermore, *Nakafuku* fails to disclose introducing a *c-myc* construct into a neural precursor cell of the adhesion culture in serum-free medium containing the first mitogen. As discussed in the interview on April 30, 2003, the MNS-57 cells in *Nakafuku* are first cultured in a medium containing serum and no mitogen. The cells are then infected with the *mycer* retrovirus. See *Nakafuku*, page 155. It is not until the cells are transfected with the *mycer* gene that bFGF is added. In addition, *Nakafuku* fails to disclose culturing the cells including the *c-myc* construct in a medium containing the first mitogen and a second mitogen that is other than the first mitogen along with a *myc*-activating chemical as required by claims 1 and 12 of the claimed invention. Therefore, Applicants respectfully submit that *Nakafuku* fails to teach or suggest each element of the claimed invention.

The Patent Office relies on *Weiss* to cure the deficiencies of *Nakafuku*. Even if *Weiss* could be combined with *Nakfuku*, which Applicant asserts is improper for reasons discussed below, the combination fails to remedy the deficiencies in *Nakafuku* to teach or suggest each and every element of claims 1 and 12 as required to support the present rejection for obviousness. As admitted by the Patent Office, although *Weiss* discloses exposing its mouse cells to a mitogen for proliferation of the cells, *Weiss* neither teaches nor suggests transfection of neural precursor stem cells with *c-myc* constructs fused to steroid/thyroid hormone receptor ligand binding domains to form stable cell lines. As in *Nakafuku*, *Weiss* also fails to disclose preparing an adhesion culture of neural precursor cells in a serum-free medium including a first mitogen followed by introducing a *c-myc* construct into a cell of the adhesion culture in serum-free medium including the first mitogen. Therefore, *Nakafuku* in combination with *Weiss* fails to teach or suggest culturing the neural precursor cells in the presence of a first mitogen before introducing a *c-myc* construct into the neural precursor cells as required in independent Claims 1 and 12.

Moreover, because *Weiss* does not disclose the use of a *c-myc* construct in its cells, it completely lacks any disclosure with respect to the addition of a *c-myc* activating chemical such as estradiol. Therefore, neither *Weiss* nor *Nakafuku* teach or suggest culturing the cells in a medium including the first mitogen and a second mitogen that is other than the first mitogen along with a *c-myc* activating chemical, as required by the claimed invention.

For at least these reasons, *Nakafuku* in combination with *Weiss* fails to teach or suggest each element of the claimed invention.

There is no motivation to combine *Weiss* with *Nakafuku*. Applicant respectfully submits that the combination of *Weiss* with *Nakafuku* is improper because the serum-free medium disclosed in *Weiss* would not have suggested to one of skill in the art at the time of the present invention an advantage to *Nakafuku*. For there to be obviousness to combine one reference with another, there must be a need or an improvement that a feature of a reference would provide the other reference to support a motivation to combine the references. *Weiss* teaches that serum-free media is critical to preserving the intrinsic differentiation potential of stem cells. *Weiss* col. 16, lines 23-26. However, there is nothing in *Nakafuku* to suggest that the differentiation potential of the *Nakafuku* stem cells is not preserved in the serum-containing medium disclosed in *Nakafuku*. *Nakafuku*, page 163. The serum-free medium of *Weiss*, therefore, would not provide any added advantage in preserving the differentiation potential of *Nakafuku* stem cells. Thus, neither *Nakafuku* nor *Weiss* suggest the desirability for their combination and, in fact, there is no motivation for the combination.

The combination of *Weiss* with *Nakafuku* is also improper because the objective of *Nakafuku* is not directed to expanding a stable cell line. *Nakafuku* discloses an immortalized multipotential neural stem cell line (MNS-57) harvested from the neural epithelium of the neural tube of an embryonic day 12 (E12) rat to study the molecular mechanisms of proliferation and differentiation of multipotential neural stem cells of the neural epithelium. The primary focus of the *Nakafuku* reference, therefore, relates to studying the molecular mechanisms underlying proliferation and differentiation of multipotential neural stems cells and, in particular, the role of the *myc* gene in proliferation and differentiation of these cells. See *Nakafuku*, page 154, first column, second paragraph. The primary focus of *Weiss*, on the other hand, is a method for the proliferation and differentiation of neural stem cells *in vitro*. Therefore, Applicants respectfully

submit that one of ordinary skill in the art would not be motivated by either *Nakafuku* or *Weiss* to combine these references.

*Nakafuku* and *Weiss* are also improperly combined because each reference teaches away from its combination. *Weiss*, for example, teaches away from its combination with *Nakafuku*. *Weiss* teaches the use of serum-free culture medium because serum tends to induce differentiation and contains unknown components. *Weiss*, Col. 16, lines 23-26. *Nakafuku*, on the other hand, supplements the culture media with serum to proliferate MNS-57 cells. Furthermore, *Weiss* teaches the use of suspension cultures instead of cultures on a fixed substrate because, according to *Weiss*, substrates tend to induce differentiation of the neural stem cell progeny. *Weiss*, Col. 16, lines 1-5. Therefore, *Weiss* expands cells in a suspension culture and initiates differentiation by plating the cells. In complete contrast to *Weiss*, *Nakafuku* teaches expanding the cells in a monolayer culture and initiating differentiation by culturing the cells in suspension. Therefore, *Weiss* essentially teaches away from the method taught by *Nakafuku*.

Not only does *Weiss* teach away from its combination with *Nakafuku*, but *Nakafuku* teaches away from its combination with *Weiss*. In *Nakafuku*, page 158, neuronal growth factor (NGF) and platelet-derived growth factor (PDGF) are taught to have “no detectable growth promoting effect on MNS-57 cells”. *Weiss*, however, teaches adding NGF and PDGF to the culture medium to influence proliferation and differentiation of the cells. This clearly constitutes a teaching away from the combination with *Weiss*.

Furthermore, in direct contrast to the teaching in *Weiss*, *Nakafuku* induces differentiation of the MNS-57 cells by suspending the cells in culture media free of proliferation-inducing growth factors such as bFGF and  $\beta$ -estradiol. In fact, the same factors, bFGF and  $\beta$ -E<sub>2</sub> are used in *Nakafuku* to not only grow the cells but to cause differentiation of those cells to occur at a much higher frequency than in cultures without the growth factors. Compare *Nakafuku*, page 159 with *Weiss*, Col. 18, lines 49-52. Therefore, *Nakafuku* teaches away from the method taught by *Weiss*.

As the Federal Circuit has established, it is improper to combine references where a reference teaches away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). “A prior art reference may be considered to teach away when a

person of ordinary skill, upon reading the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Applicant.” *Monarch Knitting Machinery Corp. v. Fukuhara Industrial Trading Co., Ltd.*, 139 F.3d 1009 (Fed. Cir. 1998), quoting, *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994). Based on the discussion above, one of skill in the art would not have been motivated to combine *Weiss* with *Nakafuku*.

Moreover, even if it would have been obvious to try to produce a stable cell line using the technique taught in *Weiss*, the Federal Circuit has held that “obvious to try” is not the standard under 35 U.S.C. §103. *Ex parte Goldgaber*, 41 U.S.P.Q.2d 1172, 1177 (Fed. Cir. 1996). “An obvious-to-try situation exists when a general disclosure may pique the scientist’s curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claim result would be obtained if certain directions were pursued.” *In re Eli Lilly and Co.*, 14 U.S.P.Q.2d 1741, 1742 (Fed. Cir. 1990).

The Patent Office also admits *Weiss* and *Nakafuku* fail to teach the use of *c-myc* constructs fused to steroid/thyroid hormone receptor ligand binding domains other than the estrogen receptor ligand binding domain. The Patent Office relies on Letters to *Nature* by Eilers (“*Eilers*”) to cure the deficiencies of *Nakafuku* and *Weiss*. However, even if the combination of the references teaches every element of the claimed invention, there is no teaching or suggestion to motivate one of ordinary skill in the art at the time of the present invention to combine *Weiss* and *Eilers* with *Nakafuku*. A rejection based on a *prima facie* case of obviousness is held improper without a motivation to combine the references. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Also, it is not enough to simply rely on the level of skill in the art to provide the suggestion to combine references as the Patent Office has done on pages 4 and 6 of the Office Action. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

To support its combination and/or modification of the cited art to arrive at the claimed invention, the Patent Office has applied hindsight reconstruction by selectively piecing together teachings of *Weiss* and *Eilers* with the teachings of *Nakafuku* in an attempt to recreate what the claimed invention discloses. Of course, as discussed above, without the requisite motivation to

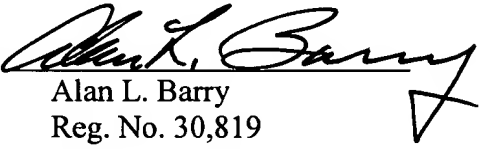
combine these teachings, this is clearly improper as being "hindsight reconstructive". See *In re O'Farrell*, 853 F.2d., 894, 902-903 (Fed. Cir. 1988).

In summary, Applicants submit that the combination of *Nakafuku* with *Weiss* is improper because there is no suggestion or motivation in either reference to combine *Weiss* with *Nakafuku*. In fact, each reference teaches away from the combination with the other. Furthermore, even if the combination is proper, the references do not teach or suggest all of the limitations found in the inventions of claims 1 and 12 as required to support the present rejection for obviousness. For these reasons the Applicant requests that the Examiner reconsider and withdraw the rejection. In addition, claims 4 and 5 depend from claim 1 and claims 15 and 16 depend from claim 12 and therefore contain all of their respective limitations and are allowable for the same reasons. Because all of the claims in the application are in proper form for allowance the applicant respectfully requests the Examiner pass the application for issuance.

Accordingly, Applicants respectfully request that the rejection of Claims 1, 4, 5, 12, 15 and 16 under 35 U.S.C. §103 be reversed.

Respectfully submitted,

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